

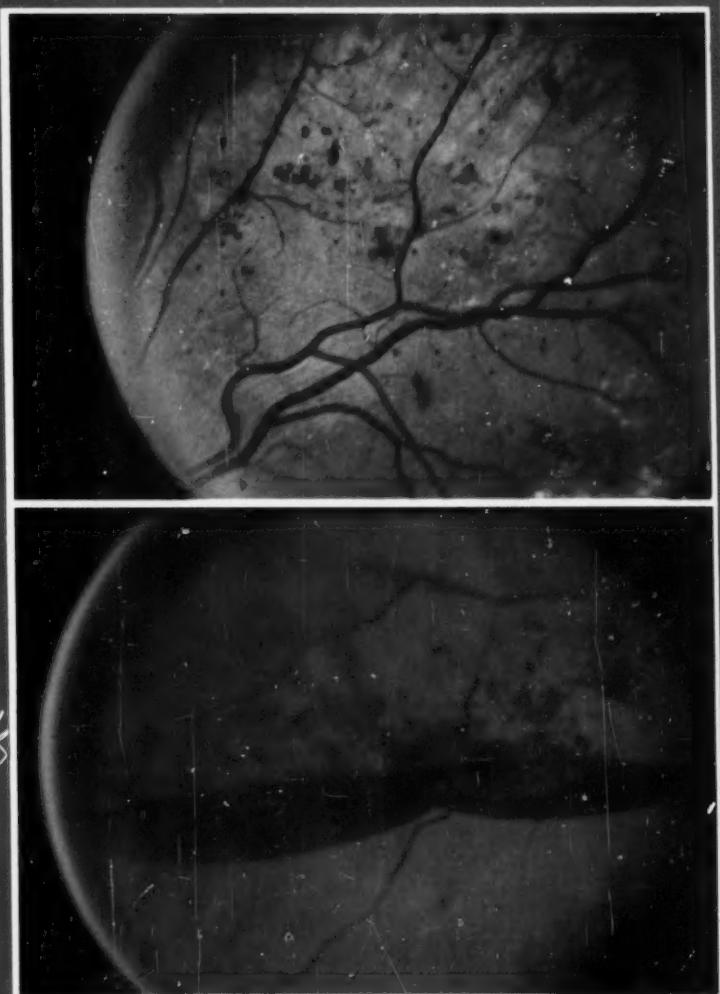
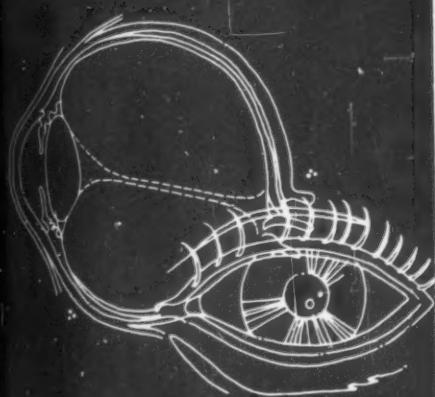
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# AMERICAN Family Physician

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Programmed Instruction  
Course on the  
Management of Diabetes

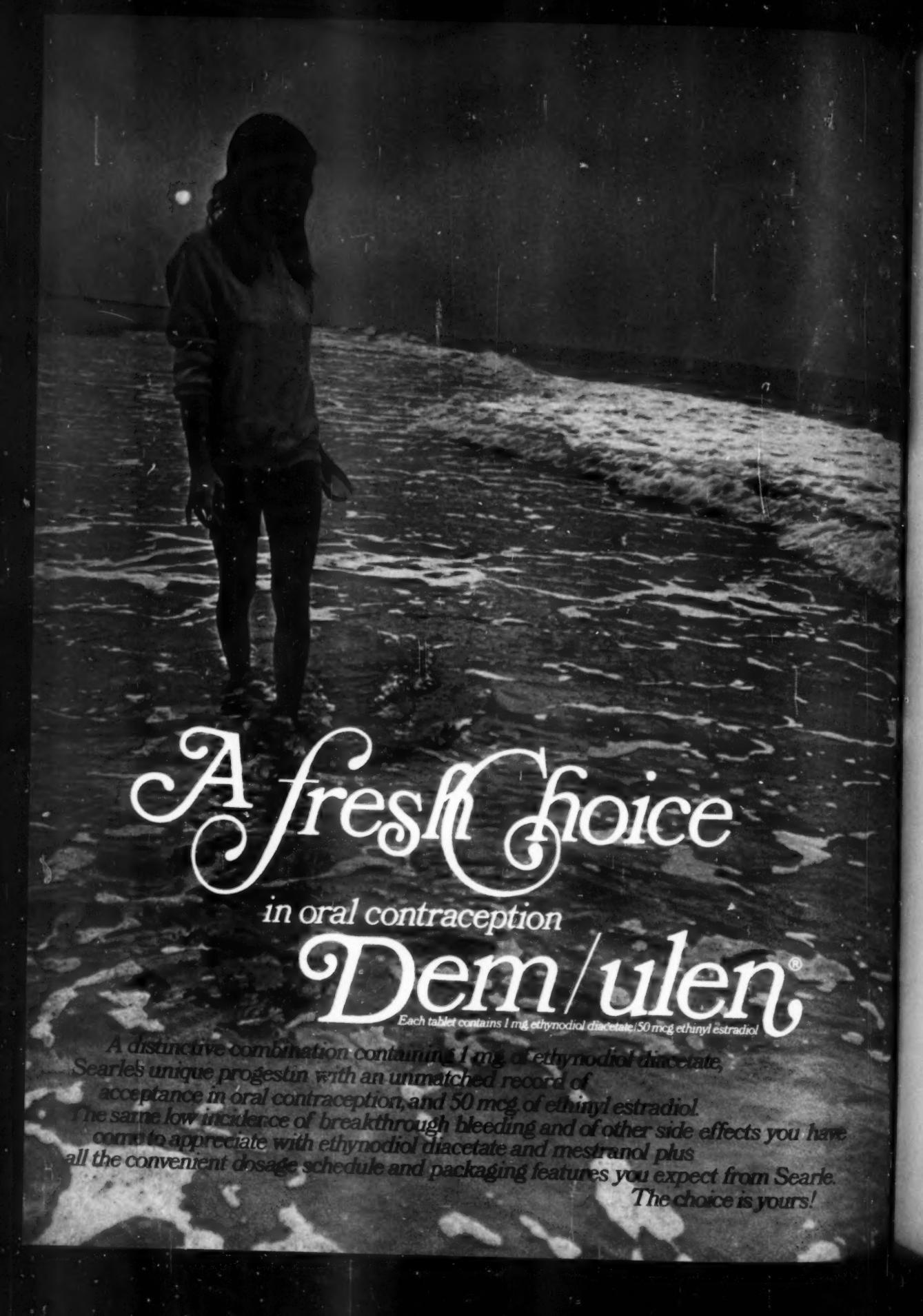
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A fresh choice  
in oral contraception  
**Demulen®**

Each tablet contains 1 mg ethynodiol diacetate/50 mcg ethynodiol estradiol

A distinctive combination containing 1 mg of ethynodiol diacetate, Searle's unique progestin with an unmatched record of acceptance in oral contraception, and 50 mcg of ethynodiol estradiol. The same low incidence of breakthrough bleeding and of other side effects you have come to appreciate with ethynodiol diacetate and mestranol plus all the convenient dosage schedule and packaging features you expect from Searle. *The choice is yours!*

# A fresh choice in oral contraception

# Demulen®

Each tablet contains 1 mg ethynodiol diacetate/50 mcg ethynodiol estradiol

**Actions**—Demulen acts to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Demulen depresses the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

**Special note:** Oral contraceptives have been marketed in the United States since 1950. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

**Indication**—Demulen is indicated for oral contraception.

**Contraindications**—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

**Warnings**—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain<sup>1-3</sup> leading to this conclusion, and one<sup>4</sup> in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll<sup>3</sup> was about sevenfold, while Sartwell and associates<sup>4</sup> in the United States found a relative risk of 4.4, measuring that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

**Precautions**—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Demulen. Therefore, if such tests are abnormal in a patient taking Demulen, it is recommended that they be repeated

after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Demulen may mask the onset of the climacteric. The pathologist should be advised of Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

**Adverse reactions observed in patients receiving oral contraceptives**—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: avolution post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in T<sub>4</sub> and T<sub>3</sub> uptake values; metyrapone test and pregnanediol determination.

**References:** 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Emolic Disease, *J. Coll. Gen. Pract.* 13: 267-279 (May) 1967. 2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, *Brit. Med. J.* 2:193-199 (April 27) 1968. 3. Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, *Brit. Med. J.* 2:651-657 (June 14) 1969. 4. Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, *Amer. J. Epidemiol.* 90:365-380 (Nov.) 1969.

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